Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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RECOMMENDATIONS AND GUIDELINES

Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19

Alex C. Spyropoulos[1] | Jerrold H. Levy[2] | Walter Ageno[3] | Jean Marie Connors[4] | Beverley J. Hunt[5] | Toshiaki Iba[6] | Marcel Levi[7] | Charles Marc Samama[8] | Jecko Thachil[9] | Dimitrios Giannis[10] | James D. Douketis[11] | on behalf of the Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis

[1]Feinstein Institutes for Medical Research and The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, and Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, NY, USA

[2]Departments of Anesthesiology, Critical Care, and Surgery, Duke University School of Medicine, Durham, NC, USA

[3]Department of Medicine and Surgery, University of Insubria, Varese, Italy

[4]Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[5]Thrombosis and Haemophilia Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK

[6]Department of Emergency and Disaster Medicine, Juntendo University, Tokyo, Japan

[7]Department of Medicine and Cardiometabolic Programme-NIHR UCLH/UCL BRC, University College London Hospitals NHS Foundation Trust, London, UK

[8]Department of Anaesthesia, Intensive Care and Perioperative Medicine GHU AP-HP. Centre—Université de Paris—Cochin Hospital, Paris, France

[9]Department of Haematology, Manchester University Hospitals, Manchester, UK

[10]Feinstein Institutes for Medical Research, Manhasset, NY, USA

[11]Department of Medicine, McMaster University, Hamilton, ON, Canada

Correspondence: Alex C. Spyropoulos, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, The Feinstein Institute for Medical Research, and Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, 130 E 77th St, New York, NY 10075 USA.
Email: aspyropoul@northwell.edu

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1 | INTRODUCTION

The novel coronavirus disease of 2019 (COVID-19) pandemic, as declared by the World Health Organization, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).[1,2] Cardiovascular disease and, in particular, venous thromboembolism (VTE), has emerged as an important consideration in the management of hospitalized patients with COVID-19. The diagnosis of VTE using standardized objective testing is problematic in these patients, given the risk of infecting non-COVID-19 hospitalized patients and hospital personnel, coupled with the usual challenges of performing diagnostic testing in critically ill patients. Early reports suggest a high incidence of VTE in hospitalized COVID-19 patients, particularly those with severe illness, that is similar to the high VTE rates observed in patients with other viral pneumonias, including severe acute respiratory syndrome

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(SARS) and Middle East respiratory syndrome (MERS-CoV).[3-6] COVID-19 is associated with marked abnormalities in markers of hypercoagulability, including elevated levels of D-dimer, fibrinogen, and factor VIII; a shortened activated partial thromboplastin time (aPTT); and an elevated sepsis induced coagulopathy (SIC) score.[7] Investigational therapies for the management of severely ill COVID-19 patients may carry an increased risk for VTE or have implications for drug-drug interactions with established agents used for the acute and chronic management of VTE, such as the direct oral anticoagulants (DOACs) and vitamin K antagonists such as warfarin.

Hospitalized COVID-19 patients share similar strong clinical intrinsic and extrinsic risk factors for VTE, including advanced age, obesity, immobility/stroke with paralysis, a history of cancer/active cancer, management in an intensive care unit (ICU)/coronary care unit (CCU) setting, a prior history of VTE or known thrombophilia, present in hospitalized medically ill patients.[7,8] However, risk stratification for VTE and the optimal intensity and duration of anticoagulant thromboprophylaxis, including post-hospital discharge prophylaxis, remains uncertain in hospitalized COVID-19 patients.

The overall objective of this guidance from the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH), developed by a multidisciplinary panel of experts in thrombosis and hemostasis, is to provide practical guidance for the management of VTE in hospitalized patients with suspected or confirmed COVID-19 infection. Specific objectives are: (a) to provide an approach to the diagnosis of VTE; (b) to provide guidance on thromboprophylaxis strategies in ICU and non-ICU settings, including the duration of prophylaxis; and (c) to provide guidance on the treatment of VTE.

2 | METHODS

This guidance statement is a collaborative effort of the Perioperative and Critical Care Thrombosis and Haemostasis Subcommittee, along with members of the Control of Anticoagulation and Disseminated Intravascular Coagulation Subcommittee of the SCC. The guidance provided is anchored on a narrative review of pertinent literature, with a search occurring until April 18, 2020, coupled with responses to a standardized and independently administered survey of preferred practices related to the diagnosis, prevention, and treatment of VTE in COVID-19 patients (Appendix S1) and conducted by the McMaster Centre for Transfusion Medicine using an independent, multi-institutional, and multidisciplinary panel of experts in the field of thrombosis and hemostasis.

The survey of experts was done using a single cross-sectional assessment approach with an expectation that all (100%) panelists would select a pre-specified management option or to indicate, through the "other option" category, that alternative management was preferred. This one-time approach, rather than a multi-step, iterative approach (eg, Delphi method), was deemed appropriate in the context of the topic (COVID-19 and thrombosis) where requisite evidence, typically used in an iterative approach, is not available. Our aim was to identify where consensus existed and, of equal importance, to identify where there was a lack of consensus on clinical management.

3 | THE DIAGNOSIS OF VTE IN HOSPITALIZED COVID-19 PATIENTS

The diagnostic assessment of suspected VTE in hospitalized COVID-19 patients is challenging, especially for critically ill patients in whom, typically, it is important to reliably confirm or exclude VTE. Imaging studies for deep vein thrombosis (DVT) or pulmonary embolism (PE) may be avoided due to concerns of transmitting infection in non-COVID-19 hospital wards or to health-care workers. The frequent finding of an elevated D-dimer in very ill hospitalized COVID-19 patients may prompt an aggressive diagnostic approach for VTE, despite the controversy that a very elevated D-dimer (>4.0 mg/L) may not be a reliable predictor of VTE in this population but rather a marker of poor overall outcome.[4,9] One recent study found a sensitivity of 85.0% and specificity of 88.5% for diagnosing VTE in patients with D-dimer levels >1.5 mg/L, but the study was based on a small sample size.[4] Bedside imaging studies such as point-of-care compression ultrasonography to assess for lower and upper extremity DVT or bedside echocardiography to assess for right ventricular strain associated with PE may be difficult to obtain due to patient instability or the requirement of prone positioning in patients with acute respiratory distress syndrome (ARDS), and may lack sufficient specificity and sensitivity to diagnose VTE as patients with pneumonia may have right ventricular strain without PE.[10] However, in the clinical context of unexplained sudden deterioration of pulmonary status or acute lower extremity erythema or swelling, these tests may be useful in aiding the clinical suspicion for VTE.

These concerns should be balanced by emerging data that the incidence of VTE in hospitalized COVID-19 patients with severe pneumonia or in ICU settings is higher than that reported by historical data in similar patients, with an incidence of VTE of 27% (95% confidence interval [CI]: 17-37) in one study using standard thromboprophylaxis and an incidence of 25% in another study without prophylaxis.[3,4] These findings are consistent with high rates of VTE in patients with other severe viral pneumonias, such as influenza H1N1, in whom there was an 18- to 23-fold higher risk for VTE compared with control patients.[5]

Some clinicians advocate in favor of routine DVT screening in hospitalized COVID-19 patients using bedside venous ultrasound based on the premise that undiagnosed DVT and resultant PE (including microthrombi-related mechanisms) may be an important contributor to hypoxic pulmonary vasoconstriction that would lead to pulmonary hypertension and right ventricular failure, in addition to worsening of ARDS. Whether routine screening with bedside venous ultrasonography or echocardiography to diagnose DVT and PE is useful in managing thromboprophylaxis strategies in sick hospitalized COVID-19 patients remains uncertain.

3.1 | Guidance statement 1

Diagnosis of VTE in hospitalized COVID-19 patients:

1. Practitioners should use standard-of-care objective testing (ie, computed tomography pulmonary angiogram [CTPA], ventilation/perfusion [V/Q] scan, magnetic resonance imaging [MRI] venography, Doppler ultrasonography) to diagnose VTE based on clinical index of suspicion. A pragmatic approach (ie, point-of-care bedside ultrasonography or echocardiography) can also be combined with standard-of-care objective testing (50% of respondents).
2. Routine screening for VTE using bedside Doppler ultrasonography of the lower extremities or based on elevated D-dimer levels is not recommended.

4 | VTE PROPHYLAXIS IN NON-ICU HOSPITALIZED COVID-19 PATIENTS

Hospitalized acutely ill medical patients, including those with infections such as viral pneumonia, are at increased risk for VTE, and antithrombotic practice guidelines recommend thromboprophylaxis with twice- or thrice-daily subcutaneous unfractionated heparin (UFH), once-daily subcutaneous low-molecular-weight heparin (LMWH), or fondaparinux to reduce this risk, although fondaparinux is infrequently used due to its long half-life and reversibility concerns.[11,12] Patients hospitalized with severe COVID-associated pneumonia may have a further heightened risk of VTE, but this issue remains unresolved. Preliminary reports in patients with severe pneumonia due to COVID-19 as well as previous reports of severe pneumonias/severe acute respiratory syndromes from other viruses such as influenza H1N1 or MERS-CoV suggest a multi-fold higher risk for VTE and, in particular, an increased risk for PE.[5] In addition, patient-specific VTE risk factors such as advanced age, a prior history of VTE, a history of or active cancer, immobility, and thrombophilia, had been incorporated prior to the COVID-19 era to assess overall VTE risk using standardized VTE risk assessment scores such as Padua VTE or IMPROVE VTE risk scores,[8,13,14] which had been externally validated.[15-17] A recent study from China in hospitalized patients with COVID-19 reported that 40% of patients had a high risk of VTE using the Padua VTE model, although the use of thromboprophylaxis was not reported.[18] The optimal VTE risk stratification scheme for hospitalized COVID-19 patients requires further study, including the use of very elevated D-dimer levels (>6 times the upper limit of normal [ULN]) that appear to be a consistent predictor of thrombotic events and poor overall prognosis in this population.[19] However, given the relatively high rates of VTE found in early reports, the use of a "universal" thromboprophylactic strategy for all hospitalized patients with COVID-19 appears more appropriate than an individualized VTE risk assessment approach at present.

All hospitalized patients with COVID-19 should be considered for thromboprophylaxis with either UFH or LMWH unless there are absolute contraindications. Advantages of LMWH over UFH include once daily versus twice or thrice daily injections and less heparin-induced thrombocytopenia. Although some DOACs are approved for in-hospital prophylaxis, these agents should be considered with caution in COVID-19 patients in whom co-administration of immunosuppressant, antiviral, and other experimental therapies may potentiate or interfere with DOAC therapy.[7] Many institutions have adopted prophylaxis protocols that use a "stepped up" or intermediate-dose LMWH regimens based on emerging evidence suggesting increased thrombogenicity with COVID-19, especially in sicker patients.[20] For patients in whom anticoagulant therapy is contraindicated, mechanical thromboprophylaxis, preferably with intermittent pneumatic compression devices, should be utilized, although there is limited evidence of efficacy in hospitalized medically ill patients.[11,21]

4.1 | Guidance statement 2

VTE prophylaxis in non-ICU hospitalized COVID-19 patients:

1. A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. Intermediate-dose LMWH may also be considered (30% of respondents).
2. VTE prophylaxis recommendations should be modified based on extremes of body weight, severe thrombocytopenia (ie platelet counts of 50 000 × 10^9 per liter or 25 000 × 10^9 per liter) or deteriorating renal function.

5 | VTE PROPHYLAXIS IN ICU HOSPITALIZED COVID-19 PATIENTS

Hospitalized COVID-19 patients who are managed in an ICU or CCU setting have an overall poor prognosis, with the proportion of severe cases approaching 26% (95% CI: 17.4-34.9) and reported case-fatality rates of 42%.[22] The presence of co-morbid conditions (eg, cardiovascular disease, obesity); a SIC score ≥ 4 and elevated levels of D-dimer (>6 times ULN), C-reactive protein, and troponins; and other markers of disseminated intravascular coagulopathy (DIC) as assessed by the ISTH scoring system are associated with a worse prognosis.[20,23] It is uncertain whether changes in hemostasis parameters are a direct consequence of the SARS-CoV2 virus or a result of a systemic inflammatory response syndrome (SIRS) that is produced by a cytokine storm after viral infection.[24] In addition, the heightened prothrombotic tendency in the critically ill hospitalized patients with COVID-19 pneumonia, leading to VTE and especially, in situ pulmonary artery microthrombi, is evident in case series and pathologic studies as an endpoint of pulmonary inflammation.[25,26] One study reported an incidence of VTE of 25% (20/81) and a mortality of 40% (8/20) among patients hospitalized with severe COVID-19 pneumonia who had VTE; another study found an incidence of VTE and arterial thromboembolism of 27% and 3.7%, respectively, in 184 COVID-19 patients

who were in an ICU setting and were receiving standard-dose thromboprophylaxis.[3,4] Last, the use of tissue plasminogen activator in the treatment of COVID-19-associated ARDS was associated with only transient improvement of pulmonary function.[27]

The optimal thromboprophylaxis strategy in the critically ill hospitalized COVID-19 patient population is uncertain. Emerging clinical data suggest that the use of either prophylactic to intermediate doses of LMWH (eg, enoxaparin, 40-60 mg daily) in very sick COVID-19 patients (D-dimer > 6 times ULN; SIC score ≥ 4) is associated with improved outcomes and a better prognosis.[20] A previous report that assessed treatment-dose UFH in patients with ARDS who were afflicted with influenza H1N1, found that patients with H1N1-associated ARDS who received therapeutic anticoagulation had 33-fold fewer VTE events than those treated given prophylactic-dose UFH or LMWH.[5] Expert clinical guidance statements and clinical pathways from large academic health-care systems favor the use of standard-dose regimens with LMWH or UFH (especially for patients with a creatinine clearance < 30 mL/min); mechanical thromboprophylaxis (intermittent pneumatic compression) when anticoagulants were contraindicated; use of multimodal (anticoagulant and mechanical) prophylaxis strategies in the critically ill and completely immobile COVID-19 population;[7,28] and the use of VTE risk stratification using either clinical criteria (body mass index [BMI] >30 kg/m^2), VTE risk scores, and/or biomarkers (eg, very elevated D-dimer levels) to suggest intermediate- or higher-dose LMWH or UFH regimens (eg enoxaparin 0.5 mg/kg twice-daily; enoxaparin 40 mg twice-daily, intravenous UFH targeted to an anti-factor Xa level of 0.30-0.70 IU/mL). Many institutional protocols of hospitalized COVID-19 patients now incorporate obesity (BMI > 30 kg/m^2) or morbid obesity (BMI > 40 kg/m^2) to administer intermediate-dose LMWH for thromboprophylaxis.[29] The use of empiric therapeutic-dose anticoagulation has been advocated by some for the critically ill hospitalized COVID-19 patients, especially in ICU settings; however, data on the efficacy and safety of this approach is limited.[3] There are ongoing randomized trials that aim to assess the efficacy and safety of more intense intermediate- to therapeutic-dose versus prophylactic-dose LMWH in hospitalized COVID-19 patients including COVID Hep (ClinicalTrials.gov Identifier: NCT04345848), Hep-COVID (ClinicalTrials.gov Identifier: NCT04401293), and The IMPACT Trial (NCT04406389).

5.1 | Guidance statement 3

VTE prophylaxis in sick ICU hospitalized COVID-19 patients:

1. Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH (50% of respondents) can also be considered in high risk patients. Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis. Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available.
2. Multi-modal thromboprophylaxis with mechanical methods (ie, intermittent pneumonic compression devices) should be considered (60% of respondents).

6 | DURATION OF THROMBOPROPHYLAXIS IN HOSPITALIZED COVID-19 PATIENTS

The risk of hospital-associated VTE extends for up to 6 weeks post-hospital discharge in high VTE risk medically ill patients, including those with pneumonia, sepsis, and any condition requiring management in an ICU setting.[30] At least 60% of all VTE events in medically ill patients occur in the post-hospital discharge period, with the first 3 weeks being associated with a >five-fold increased risk in fatal PE.[14] Earlier studies of extended thromboprophylaxis with DOACs revealed either limited efficacy or an increase in major bleed risk, and particularly due to these safety concerns, the most recent antithrombotic guidelines recommended against routine post-discharge thromboprophylaxis in medically ill patients, including those with pneumonia.[12] However, more recent data reveal that in selected populations at high VTE risk and low bleed risk, based on key risk factors or risk models for thrombosis and bleeding, extended-duration thromboprophylaxis for approximately 4 weeks with prophylactic-dose LMWH (eg, enoxaparin, dalteparin, tinzaparin) or a DOAC (eg rivaroxaban, betrixaban) provides a net clinic benefit by reducing VTE risk without incurring a significant increase in the risk of major bleeding.[31-33] This benefit appears more pronounced in patients whose index hospitalization was due to infectious disease, particularly pneumonia.[34] Recent data also support that a modified IMPROVE VTE score using established cut-offs plus elevated D-dimer (>2 times ULN) identifies patients at an almost three-fold higher risk for VTE in whom there is a significant benefit for extended-duration thromboprophylaxis.[35] This finding may be especially relevant for post-discharge VTE risk mitigation in COVID-19 patients. In the absence of COVID-19-specific data, it is reasonable to consider extended-duration thromboprophylaxis with LMWH or a DOAC for at least 2 weeks and up to 6 weeks post-hospital discharge in selected COVID-19 patients who are at low risk for bleeding and with key VTE risk factors such as advanced age, stay in the ICU, cancer, a prior history of VTE, thrombophilia, severe immobility, an elevated D-dimer (>2 times ULN), and an IMPROVE VTE score of 4 or more.

6.1 | Guidance statement 4

Duration of VTE prophylaxis for hospitalized COVID-19 patients:

1. Either LMWH (30%) or a DOAC (ie, rivaroxaban or betrixaban; 30% of respondents) can be used for extended-duration thromboprophylaxis.
2. Extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria. The duration of post-discharge thromboprophylaxis can be approximately 14 days at least (50% of respondents), and up to 30 days (20% of respondents).

7 | VTE TREATMENT IN HOSPITALIZED COVID-19 PATIENTS

There are multiple validated and approved strategies to treat hospitalized patients with a new VTE including the use of UFH/LMWH bridging therapy to dose-adjusted warfarin, the use of UFH/LMWH lead-in therapy with a switch to dabigatran/edoxaban, or a monotherapy approach with rivaroxaban/apixaban.[36] In hospitalized COVID-19 patients, parenteral anticoagulation with UFH or LMWH may have advantages over other strategies due to the absence of known drug-drug interactions with antiviral agents or investigational therapies used to treat COVID-19. Moreover, the use of LMWH may have further advantages in this setting due to lack of routine monitoring and decrease of health-care worker exposure to infection due to frequent blood draws necessary with intravenous UFH, which may require higher-than-usual doses from possible heparin resistance due to acute phase reactants. DOACs may also have further disadvantages in this setting due to potential drug-drug interactions via CYP3A4 mechanisms with certain antivirals (ie, lopinavir/ritonavir) and immunomodulatory investigational COVID-19 therapies, as well as potential for lack of reversal agents or specific antidotes in some hospitals.[7,28] However, in the post-hospital discharge setting, DOACs provide advantages over vitamin K antagonists such as warfarin due to the lack of need for routine monitoring and subsequent minimization of patient contact with the health-care environment.

7.1 | Guidance statement 5

VTE treatment in hospitalized COVID-19 patients:

1. Established guidelines should be used to treat patients with confirmed VTE, with advantages of LMWH in the inpatient setting and DOACs in the post-hospital discharge setting. A change from treatment-dose DOAC or vitamin K antagonists (VKA) to in-hospital LMWH should be considered especially for patients in critical care settings or with relevant concomitant medications, and dependent on renal function and platelet counts. Anticoagulant regimens should not change based solely on D-dimer levels.
2. A change of anticoagulant regimen (ie, from prophylactic or intermediate-dose to treatment-dose regimen) can be considered in patients without established VTE but deteriorating pulmonary status or ARDS (50% of respondents).
3. The duration of treatment should be at least 3 months (50% of respondents).

8 | DISCUSSION

COVID-19 is emerging as a highly contagious disease with coagulopathic manifestations that appear to have unique characteristics. Initial data support a high incidence of thromboembolic disease, and especially VTE, in hospitalized COVID-19 patients, as well as poorer outcomes for COVID-19 patients with pre-existing cardiovascular disease.[3,7] Due to the risk of infectivity with a need to minimize contact with health-care workers and the health system; the diagnosis of VTE in critically ill, unstable hospitalized COVID-19 patients (especially in the ICU) that may need prone positioning and may not be able to undergo standard objective testing; the potential for new VTE risk stratification strategies using novel dosing intensities of established thromboprophylaxis regimens; new paradigms of post-hospital discharge and extended thromboprophylaxis; and careful considerations of antithrombotic management due to the potential for drug-drug interactions with investigational or immunomodulatory therapies, health-care workers will need to understand special considerations for the management of VTE in hospitalized COVID-19 patients.

There is an urgent need for high quality data, especially from randomized controlled trials, using a coordinated effort by health-care

TABLE 1 Key management issues for VTE in hospitalized COVID-19 patients

Topic
Diagnosis of VTE
What is the optimal diagnostic strategy in sick hospitalized patients?
Should practitioners use elevated D-dimer to guide diagnosis of VTE?
Prophylaxis of VTE
Should practitioners use VTE risk stratification, including D-dimer, to determine optimal thromboprophylaxis strategy?
Should practitioners use higher than usual (ie, intermediate) doses of UFH/LMWH for VTE prophylaxis? Higher than usual dose (ie 50% increased) in obese patients?
Should practitioners use empiric treatment dose UFH/LMWH in the management of sick patients (ie, D-dimer > 6 × ULN, elevated SIC scores)?
Duration of thromboprophylaxis
What clinical/biomarker criteria and which VTE RAM should practitioners use for extended thromboprophylaxis?
What is the optimal agent/duration of extended thromboprophylaxis?
Treatment of VTE
What is the optimal agent and duration for VTE treatment? In-hospital? In the outpatient setting?

funding agencies, organizations dedicated to thrombotic disorders, and professional societies, to answer some of the most urgent questions. These urgent questions are included in Table 1. There is currently one large international registry on VTE (RIETE) that is capturing data elements for COVID-19 patients with VTE, and other ongoing registries (CORONA-VTE and CORE-19) that are capturing hospital and post-hospital discharge data elements for patients with COVID-19. There is also a new registry by the American Heart Association planned for cardiovascular outcomes of these patients. Last, ongoing and planned randomized trials will address key clinical questions, especially the effect of anticoagulation on outcomes in critically ill COVID-19 patients and whether more intense thromboprophylaxis strategies improve morbidity and mortality in hospitalized COVID-19 patients.

This guidance document, using a consensus-based approach, has attempted to provide useful directions for health-care practitioners managing VTE-related issues in hospitalized COVID-19 patients. We acknowledge that the lack of an iterative process in our survey produced some guidance statements that may not have been supported by a majority of expert panel members. As more data is forthcoming, especially high quality data, there needs to be rapid dissemination of these data that addresses some of the most urgent clinical issues in this patient population.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Alex C. Spyropoulos contributed to the concept, analysis/interpretation of data, critical writing, and revising intellectual content. Jerrold H. Levy contributed to the concept, interpretation of data, and revision of intellectual content. Walter Ageno contributed to the concept, interpretation of data, and revision of intellectual content. Jean M Connors contributed to the concept, interpretation of data, and revision of intellectual content. Beverley J. Hunt contributed to the concept, interpretation of data, and revision of intellectual content. Toshiaki Iba contributed to the concept, interpretation of data, and revision of intellectual content. Marcel Levi contributed to the concept, interpretation of data, and revision of intellectual content. Charles Marc Samama contributed to the concept, interpretation of data, and revision of intellectual content. Jecko Thachil contributed to the concept, interpretation of data, and revision of intellectual content. Dimitrios Giannis contributed to the concept, interpretation of data, and revision of intellectual content. James D. Douketis contributed to the concept, analysis/interpretation of data, critical writing, and revision of intellectual content.

ORCID

Alex C. Spyropoulos https://orcid.org/0000-0002-3175-461X
Jean Marie Connors https://orcid.org/0000-0001-6445-582X
Beverley J. Hunt https://orcid.org/0000-0002-4709-0774
Dimitrios Giannis https://orcid.org/0000-0001-9246-976X
James D. Douketis https://orcid.org/0000-0001-5288-0394

TWITTER

Alex C. Spyropoulos @AlexSpyropoul

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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